Guidelines on monitoring the safety profile of tafenoquine for healthcare professionals in Thailand

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Preface

Malaria is an important public health problem in Thailand. Thailand has launched and implemented measures in all endemic areas for all population at risk to control and prevent this disease.[1] These have resulted in the decreased numbers and rates of malaria patients consisting of patients with *Plasmodium vivax* malaria who are the majority cases of malaria in Thailand.

Tafenoquine is an antimalarial medicine for the prophylaxis and treatment of *P. vivax* infection. This medicine has been approved by four countries, namely the U.S., Australia, Brazil and Thailand. It was firstly approved by the U.S. Food and Drug Administration (FDA) in 2018. There were approximately 4,000 patients involving phases I – III clinical trials of tafenoquine. With this small number of participants, the safety profile of tafenoquine is thus limited. Monitoring the safety profile of this medicine after the approval of tafenoquine is needed.

The World Health Organization (WHO) would like to strengthen pharmacovigilance system in low and middle-income countries and then launched the Smart Safety Surveillance (3S) project. Tafenoquine, which is a new medicine, is used as a pilot for this project. It requires active surveillance or enhanced pharmacovigilance surveillance to monitor its safety profile. The WHO invited the Health Product Vigilance Center (HPVC), the Thai FDA to participate in the 3S project to monitor the safety profile of tafenoquine.

These guidelines on monitoring the safety profile of tafenoquine are issued owing to the 3S project. They will help healthcare professionals conduct active surveillance of tafenoquine and report its adverse events to the HPVC, the Thai FDA.

We hope that these guidelines will be useful to healthcare professionals in monitoring the safety profile of tafenoquine. We would like to thank all healthcare professionals who have collaborated with us in monitoring the safety profiles of all health products and reporting adverse events to the HPVC. Finally, we hope that healthcare professionals will help us send adverse event reports associated with tafenoquine to the Thai FDA. We will use this information to improve patient safety.

Thai Food and Drug Administration

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Chapter 1
Introduction

Malaria is a mosquito-borne infectious disease. It is an important public health problem in Thailand. Most of the initial symptoms of malaria are not specific. Fever is mostly found after the initial mosquito bite for 1 – 2 weeks. The duration can be longer in case of *Plasmodium malariae* infection which has 1-month onset.[2]

Typical symptoms of malaria include fever, chilling, headache and tiredness.[3] Malaria can be cured if patients are corrected and timely diagnosed and receive proper treatment. If not, their symptoms may be severe or they die due to its complications such as liver failure, renal failure and cerebral malaria especially patients with *P. falcipalum* infection.[3]

Malaria in human is caused by protozoan parasites *P. falciparum, P. vivax, P. malariae, P. ovale* (consisting of two subspecies -- *P. ovale curtisi* and *P. ovale wallikeri*) or *P. knowlesi.*[2] In Thailand, *P. vivax* and *P. falciparum* account for the majority cases of malaria.

Thailand aims to eliminate malaria. Thus, Thailand launches measures which have been implemented in all endemic areas for all population at risk.[1] These have resulted in decreasing the numbers and rates of malaria patients. There were 35,912 patients with malaria in 2012 and 5,413 in 2019. (Table 1)

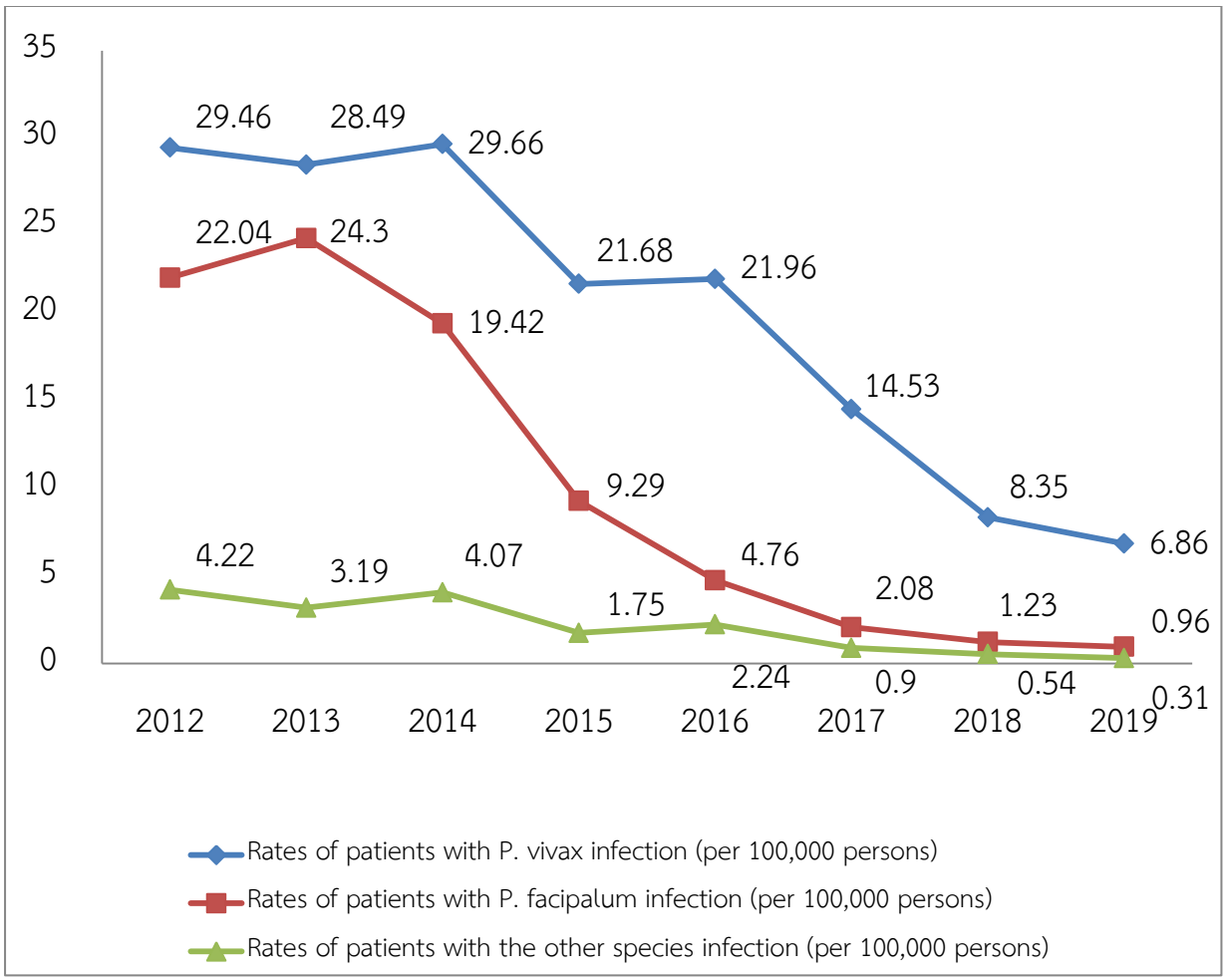
Table 1 Numbers of patients with malaria during 2012 – 2020 (as of 10th March 2020)[4]

Year	Protozoan parasite						Unknown	Total
	V	F	M	K	O	Mix		
2012	18,986	14,209	92	-	-	237	2,388	35,912
2013	18,456	15,741	71	-	2	174	1,821	36,265
2014	19,318	12,645	60	-	4	194	2,390	34,611
2015	14,249	6,105	51	-	-	198	899	21,502
2016	14,477	3,137	37	1	1	127	1,313	19,093
2017	9,615	1,374	32	6	-	80	480	11,587
2018	5,547	817	32	31	-	76	220	6,723
2019	4,568	637	45	19	-	37	107	5,413
2020 (as of 10/3/2020)	357	26	7	-	-	5	16	411

Notes V = *P. vivax,* F = *P. falciparum,* M= *P. malariae,* K = *P. knowlesi* and O = *P. ovale*

The rate of malaria infection due to *P. vivax* was 29.46 patients per 100,000 persons in 2012. After the implementation of the measures, the rates of malaria infection have decreased. There were 6.86 patients per 100,000 persons in 2019. (Figure 1) According to statistics from the Thai Department of Disease Control, the first five ranked provinces with high numbers of patients with *P. vivax* infection in 2019 consist of Yala (1,192 patients), Tak (470 patients), Kanchanaburi (218 patients), Mae Hong Son (189 patients) and Phetchaburi (165 patients).

Figure 1 Rates of patients with malaria per 100,000 persons by malaria species and years



The World Health Organization (WHO) recommends that after patients with *P. vivax* infection receive standard antimalarial treatment, they should receive daily doses of primaquine for 14 days to prevent relapses of the infection. Therefore, drug compliance for taking primaquine is very important.[5] Tafenoquine is a new medicine for *P. vivax* treatment. It can also prevent relapse of *P. vivax infection* like primaquine but patients with this disease take only a single dose. Thus, it may increase the likelihood of treatment compliance. However, the safety profile of tafenoquine is very limited because it has been recently approved. Both primaquine and tafenoquine can cause a serious adverse drug reaction which is hemolytic anemia in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency. Since the half-life of tafenoquine is much longer than that of primaquine, the management of this reaction in patients treated with tafenoquine is more difficult.

The WHO realizes the importance of active surveillance of tafenoquine. Since Thailand has a good pharmacovigilance system, the WHO invited the Health Product

Vigilance Center (HPVC) -- the Thai National Pharmacovigilance center, Ministry of Public Health to join the Smart Safety Surveillance (3S) in order to monitor the safety profile of tafenoquine. The Ministry accepted the invitation in 2019.

Pharmacovigilance in Thailand involves various sectors (e.g. health facilities, hospitals and pharmaceutical companies) which work as a pharmacovigilance network. However, healthcare professionals in hospitals have an important role in reporting adverse events to the HPVC. Most of adverse event reports in the HPVC database (Thai Vigibase) are reported by them. The reports in the Thai Vigibase are used as an important resource for launching proper risk management of medicines. The Thai Food and Drug Administration (FDA) approved tafenoquine as a conditionally approved new drug on 27th December 2019.[6] An important adverse drug reaction of tafenoquine is hemolytic anemia in patients with G6PD deficiency. Therefore, patients with *P. vivax* infection must be tested their G6PD activity before taking tafenoquine. The half-life of tafenoquine is about 2 – 3 weeks and information on the safety profile of tafenoquine is very limited. Thus, it requires active surveillance for monitoring the safety profile of tafenoquine. The HPVC prepares these guidelines for healthcare professionals to help them to conduct active surveillance for tafenoquine.

1. Objectives

The objectives of these guidelines are to help healthcare professionals to monitor the safety profile of tafenoquine and report its adverse events to the HPVC, the Thai FDA during 2020 – December 2022.

2. Definitions

2.1 Adverse event (AE)

An adverse event is any symptom or outcome suspected of being associated with the use of a health product resulting in danger to the human body, regardless of whether it is the result of intentional or accidental overdose, misuse, defect of the product or cessation of use. The event may or may not be causally related to the use of the health product. Health products are defined as foods, drugs, biologics, vaccines, herbal drugs, narcotics, psychotropic substances, cosmetics, medical devices or hazardous substances used in households and public health.

2.2 Serious adverse event

Serious adverse event (experience) or reaction is any untoward medical occurrence that at any dose. It means any adverse event of the following categories:

1) Death means any death that is suspected to be the result of an adverse event caused by using the suspected health product. This does not include death with a certain link with fetal death or abortion attributed to congenital anomaly or miscarriage.

2) Life-threatening means the patient is at substantial risk of dying at the time of the adverse event, or use or continued use of the health product. It may result in patient death. Examples include anaphylactic shock and apnea.

3) Hospitalization–initial/prolonged means the adverse event is the cause of the patient's hospitalization or prolonged hospitalization. (If the patient needs only observation in the emergency room, without admission, the reporter can choose "other medically important condition".)

4) Persistence or significant disability/incapacity means the adverse event results in a substantial disruption of a person's ability to conduct normal life functions. It leads to a significant, persistent or permanent change, impairment, damage or disruption in the patient's body function/structure, physical activities and/or quality of life such as blindness and renal failure.

5) Congenital anomaly/birth defect means the health product that the patient used before or during pregnancy may have resulted in fetal congenital anomaly or birth defect.

6) Other medically important condition means the adverse event does not fit the other categories, but the adverse event may harm the patient and may require medical or surgical intervention (treatment) in order to prevent one of the other categories of outcomes. For examples, this category includes allergic bronchospasm (a serious problem with breathing) requiring medical treatment in an emergency room, blood dyscrasias and seizures/convulsions not resulting in hospitalization.

2.3 Adverse Drug Reaction (ADR) means an unintended reaction which is harmful to the human body. It occurs when the drug is used at a normal dose for the prophylaxis, diagnosis or treatment of disease or to change the body's physiology, not including any result from an unintentional or accidental overdose, use or misuse.

2.4 Outcome after the adverse event (sequelae):

Recovered without sequelae means after the adverse event, the patient recovered completely without any remaining symptom or lesion as the consequence of the adverse event.

Recovered with sequelae means after the adverse event, the patient had a normal recovery, but still had some remaining symptom or lesion resulting from the adverse event.

Recovering means after the adverse event, the patient is covering but is still suffering some adverse event.

Not yet recovered means after the adverse event, on the day of reporting, the patient is still suffering some adverse event.

Death is one of the followings.

1) Due to adverse event means the adverse event resulted in death of the patient. It also includes death caused by the complications that followed an adverse event, for example a patient had Steven–Johnsons syndrome after taking co–trimoxazole and later died from sepsis. For this case, death is attributed to the adverse event because the complication that caused the patient's death had developed from Steven–Johnsons syndrome.

2) Drug may be contributory means death was the outcome after the adverse event, but the cause of death may be attributed to other associated factors, one of which is the adverse event. Death may be the result of the combination of the patient's underlying disease and taking the suspected product. For example, a patient who had the underlying disease of ventricular arrhythmia, died from ventricular arrhythmia after taking cisapride. For this case, there were two factors associated with the patient's death - underlying disease and cisapride.

3) Unrelated to drug means outcome after the adverse event was the patient's death, attributable to other causes such as chronic disease or disease that resulted in hospitalization, not associated with any health product use. For example, a brain abscess patient had a pruritic rash after receiving cloxacillin injection during the treatment of the drug allergy, the patient died from the brain abscess.

Loss of follow up means no knowledge of the outcome after the adverse event.

2.5 Causality assessment evaluates the level of the probability of the relationship between the suspected drug and the adverse reaction classified into 5 levels, as follows.

Certain means the adverse reaction (clinical symptoms and positive laboratory findings) has the following characteristics.

(1) occurred during the time which corresponds with the use of the drug and

(2) cannot be explained by a pre-existing disease or by a concomitantly used drug or other chemical substance and

(3) the adverse reaction obviously improved or disappeared after the patient stopped using the drug and

(4) when the drug was used again, the adverse reaction recurred and could be explained by pharmaceutical mechanism or the adverse event is clearly evident.

Probable means the adverse reaction (clinical symptoms and positive laboratory findings) has the following characteristics.

(1) occurred during the time which corresponds with the use of the drug and

(2) probably not associated with a pre-existing disease or a concomitantly used drug or other chemical substance and

(3) when the patient stopped using the drug the adverse reaction improved or disappeared but

(4) information about repeat drug use may not be available

Possible means the adverse reaction (clinical symptoms and positive laboratory finding has the following characteristics.

(1) occurred during the time which corresponds with the use of the drug but

(2) may be explained by pre-existing disease or by concomitant used drug or other chemical substance and

(3) information about the patient stopped use of the drug is not complete or not available

Unlikely means the adverse reaction (clinical symptoms and positive laboratory finding has the following characteristics.

(1) occurred during the time which does not correspond with the use of the drug and

(2) cannot be explained by a pre-existing disease or by a concomitantly used drug or other chemical substance

Unclassified means there is no available information to show the connection between the health product and the adverse event.

Chapter 2
Tafenoquine information

The HPVC, the Strategy and Planning Division, the Thai FDA has participated in the Smart Safety Surveillance (3S) Project according to the invitation of the WHO to conduct active surveillance of tafenoquine. It is an antimalarial medicine for the prophylaxis and treatment of *P. vivax* infection.

Tafenoquine is an 8-aminoquinoline derivative medicine. It is used for *P. vivax* infection in all stages including the hypnozoite stage which is the presence of hypnozoites in the liver. This stage results in relapsing the disease even if there is no *P. vivax* in the blood of the patient. Relapsing of the disease can occur after the infection 3 – 6 weeks to several months (6 – 12 months).[7]

The Thai FDA authorizes tafenoquine as a conditional approval new drug. It is indicated for the treatment of *P. vivax* infection and prevention of relapsing the disease in patients aged 16 years.[6] Patients take tafenoquine for only a single dose since it has the long half-life (approximately 2 – 3 weeks). According to the 2019 Thai Clinical Practice Guidelines on the treatment of malaria, it recommends taking primaquine for the treatment of the hypnozoite stage of *P. vivax* infection for 14 days.[3] This long duration period of the treatment may lead to poor drug compliance.

Tafenoquine approvals

Currently, tafenoquine has been authorized for the prophylaxis and treatment of *P. vivax* malaria by four countries as described in Table 2.

Table 2 Tafenoquine approvals

Country	Trade name	Market authorization holder	Approval date	Indications
the U.S.	Krintafel® tablet 150 mg[8]	GlaxoSmithKline	20th July 2018	Radical cure (prevention of relapse) of *P.vivax* malaria in patients aged at least 16 years receiving appropriate antimalarial treatment for acute *P.vivax* infection
	Arakoda® tablet 100 mg[9]	60 Degrees Pharmaceuticals, LLC	8th August 2018	Prophylaxis of malaria in patients aged at least 18 years
Australia[10]	Kozenis® tablet 150 mg[11]	GlaxoSmithKline	12th September 2018	Radical cure (prevention of relapse) of *P.vivax* malaria in patients aged at least 16 years receiving appropriate antimalarial treatment for acute *P.vivax* infection
	Kodatef® tablet 100 mg[12]	Biocelect Pty Ltd	12th September 2018	Prevention of malaria in adults aged at least 18 years for up to 6 months of continuous dosing
Brazil	Kozenis®[13]	GlaxoSmithKline	October 2019	Radical cure (prevention of relapse) of *P. vivax* malaria in patients aged at least 16 years receiving chloroquine for acute *P. vivax* infection
Thailand	Kozenis® tablet 150 mg[6]	GlaxoSmithKline	27th December 2019	Radical cure (prevention of relapse) of *P.vivax* malaria in patients aged at least 16 years

Pharmacokinetics[8]

Absorption

Time to maximum plasma concentrations (T_{max}), oral administration: 12 - 15 hours

Food effect: When administered an investigational capsule formulation with a high-calorie and high-fat meal (approximately 1,000 calories with 15% protein, 25% carbohydrate, and 60% fat), the plasma area under the curve (AUC) of the medicine increased by 41% and maximum plasma concentration (C_{max}) increased by 31% compared with the fasted condition.

Drug distribution

Protein binding: > 99.5%.

Volume of distribution (Vd): 1,600 liters.

Elimination

Oral clearance: 3 liters/hour

Half-life: approximately 15 days

Metabolism: The metabolism of tafenoquine is very slow.

Excretion: The full excretion profile of tafenoquine in humans is unknown. However, over a 6-day collection period, renal elimination of unchanged tafenoquine is low.

Special populations

The pharmacokinetics of tafenoquine are not significantly affected by age, sex, ethnicity and body weight. However, knowledge of the impact of renal or hepatic impairment on the pharmacokinetics of tafenoquine is still unclear.

Drug interaction

Tafenoquine should be avoided coadministration with organic cation transporter-2 (OCT2) and multidrug and toxin extrusion (MATE) substrates such as dofetilide and metformin. If coadministration cannot be avoided, drug-related toxicities of the coadministered drugs should be monitored. Moreover, reducing the dose of the coadministered drugs may be needed based on the approved product labeling.

Indications, dosage and administration

Tafenoquine is indicated for the radical cure (prevention of relapse) of *P. vivax* malaria in patients at least aged 16 years by taking a single dose of 300 mg.

Criterion for prescribing tafenoquine

All patients must be tested for G6PD status before prescribing tafenoquine by physicians using quantitative G6PD test. Patients having a G6PD enzyme activity level > 6 IU/gHb (>70%) can be dispensed with a tafenoquine 300-mg single dose.[3]

Contraindication[8,9]

Tafenoquine is contraindicated in

- Patients with G6PD deficiency or unknown G6PD status since it can cause hemolytic anemia.
- Women breastfeeding an infant with G6PD deficiency or unknown G6PD status.
- Patients with a history of psychotic disorder or current psychotic symptoms (hallucinations, delusions and/or grossly disorganized behavior).
- Patients with known hypersensitivity to tafenoquine, any component of tafenoquine or other 8-aminoquinolines.

Warnings and precautions[8,9]

Hemolytic anemia

Patients must be tested for G6PD status before starting tafenoquine since patients with G6PD deficiency taking tafenoquine may experience hemolytic anemia. Owing to the limitation of G6PD tests, physicians have to be aware of the risk of hemolysis and prepare adequate medical support to manage and follow up the risk.

Tafenoquine is contraindicated in patients with G6PD deficiency or unknown G6PD status. In clinical trials, some patients with normal G6PD activity levels still had decreased hemoglobin levels. Therefore, patients receiving tafenoquine should be monitored for clinical signs and symptoms of hemolysis. Patients are advised to seek medical attention if signs of hemolysis occur. Due to the long half-life of tafenoquine, the signs of hemolysis that patients may experience could be delay in onset and/or duration.

G6PD Deficiency in pregnancy or lactation

Even though a pregnant woman has normal G6PD activity levels, the fetus could be G6PD deficient. The fetus with G6PD deficiency may experience hemolytic anemia when a pregnant woman receiving tafenoquine. Therefore, the use of tafenoquine is not

recommended during pregnancy. Moreover, females of reproductive potential should avoid pregnancy or receive effective contraception for 3 months after taking tafenoquine.

An infant with G6PD-deficiency or unknown G6PD status is contraindicated to be breastfed from a mother taking tafenoquine. Since an infant with G6PD-deficiency may experience hemolytic anemia from exposure to tafenoquine through breast milk, the infant's G6PD status must be examined before starting breastfeeding.

Methemoglobinemia

Clinical trials of tafenoquine found asymptomatic increases in blood methemoglobin. It recommends that patients with nicotinamide adenine dinucleotide (NADH)-dependent methemoglobin reductase deficiency receiving tafenoquine should be carefully monitored. When they have signs of methemoglobinemia, appropriate therapy should be provided to them.

Psychiatric Effects

In clinical trials of tafenoquine, psychiatric adverse drug reactions including anxiety (3%), abnormal dream (<1%), insomnia (3%) were observed in patients receiving tafenoquine. Two cases of depression and two cases of psychosis occurred in patients with a history of psychiatric disorders after taking 350-600-mg single dose of tafenoquine. These doses were higher than the approved dose (300 mg). Before prescribing tafenoquine in patients with a history of psychiatric conditions, the benefit of treatment has to be weighed against the risk of psychiatric adverse reactions. Due to the long half-life of tafenoquine (approximately 15 days), psychiatric adverse reactions may delay in onset and/or duration.

Hypersensitivity reactions

Patients receiving tafenoquine may experience serious hypersensitivity reactions (e.g. angioedema and urticaria). If hypersensitivity reactions occur, the patients have to be provided with proper therapy. Moreover, they must not be re-administered with tafenoquine. This medicine is contraindicated in patients with a history of hypersensitivity to tafenoquine, any component of tafenoquine or other 8-aminoquinolines.

Due to the long half-life of tafenoquine (about 15 days), signs and symptoms of hypersensitivity adverse reactions could be delayed in onset and/or duration. Patients are advised to seek medical attention if signs of hypersensitivity develop.

Adverse drug reactions[8,9]

Table 3: Adverse drug reactions associated with tafenoquine

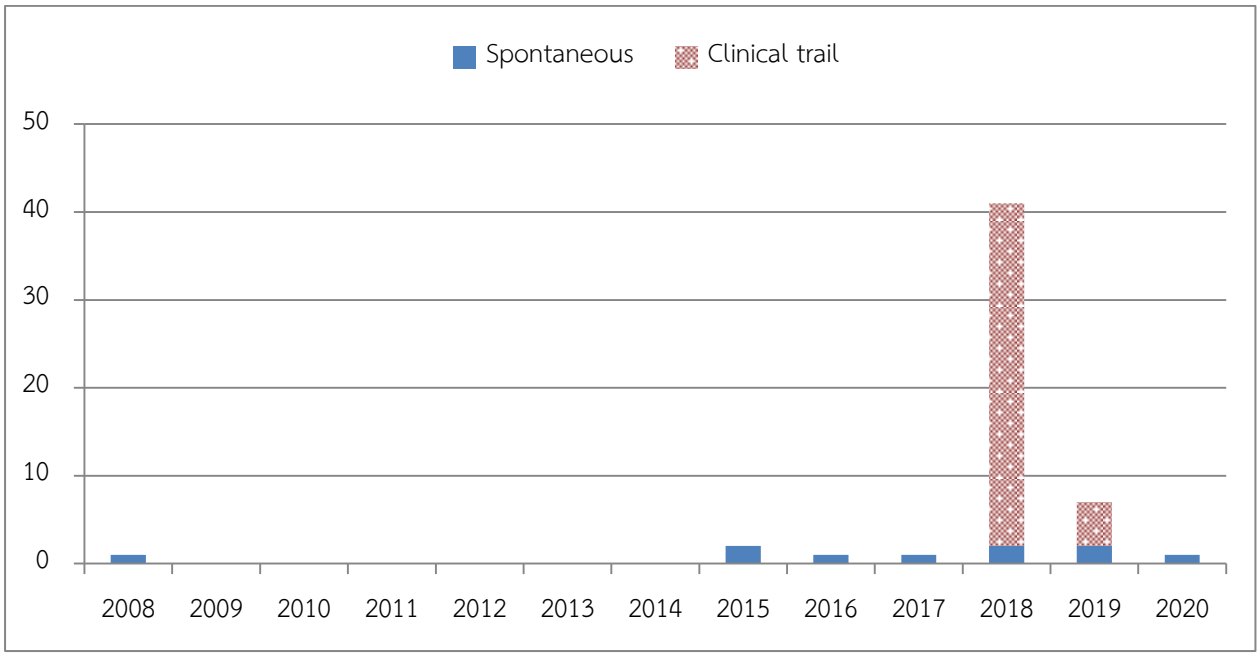
System organ class	Adverse drug reactions
Blood and lymphatic system disorders	Hemolytic anemia, anemia, thrombocytopenia
Ear and labyrinth disorders	Motion sickness, vertigo, positional vertigo, hyperacusis, Meniere's disease
Eye disorders	Night blindness, photophobia, blurred vision, reduced visual acuity, visual impairment, vitreous floaters, Vortex keratopathy, keratopathy, retinal disorder, retinal abnormality.
Gastrointestinal disorders	Gastrointestinal disturbance, diarrhea, nausea, abdominal pain, vomiting, methemoglobinemia
Hepatobiliary disorders	Hyperbilirubinemia, cholestatic jaundice
Immunologic system disorders	Hypersensitivity reactions (e.g., angioedema and urticaria).
Laboratory investigations	Increased / abnormal Alanine Aminotransferase (ALT), increased blood creatinine, increased blood methemoglobin, increased blood bilirubin, decreased glomerular filtration rate, decreased hemoglobin.
Musculoskeletal and connective tissue disorders	Back pain
Nervous system disorders	Headache, sinus headache, migraine, tension headache, dizziness, postural amnesia, abnormal coordination, hyperesthesia, hypoesthesia, motion sickness, somnolence, syncope, tremor, visual field defect.
Psychiatric disorders	Sleep disturbance, abnormal dreams, insomnia, nightmares, sleep disorder, somnambulism, depression/depressed mood, anxiety, panic attack, stress, agitation, neurosis
Skin and subcutaneous tissue disorders	Urticaria, pruritus

Chapter 3

Adverse drug reactions associated with tafenoquine in the global database

The WHO VigiBase™ is the WHO global database of individual case safety reports (ICSRs), submitted by member countries of the WHO Program for International Drug Monitoring (PIDM). The Uppsala Monitoring Center (UMC), the WHO Collaborating Centre for PIDM, is responsible for managing and updating the database.[14] As of 25th February 2020, 54 reports of suspected adverse drug reactions of tafenoquine were received from three countries including Australia 51 reports (94.4 %), Cambodia two reports (3.7 %) and the U.S. one report (1.9 %). Fourth-four of them are from clinical trials, the rest (10) were spontaneous reports. All of these reports were submitted during 2008 - 2020 (Figure 2).

Figure 2 Numbers of adverse drug reaction reports associated with tafenoquine by types of reports and years in the WHO VigiBase™



Psychiatric system disorders (88.9 %) were the most common adverse reaction reported with tafenoquine, followed by nervous system disorders (75.9 %), general disorders and administration site conditions (42.6 %), gastrointestinal (33.3 %) and systems ear and labyrinth therapy disorders (31.5%) as shown in Table 4.

Table 4 Numbers of adverse drug reactions associated with tafenoquine by system organ classes in the WHO VigiBase™

System organ class	Number	Percentage
Psychiatric disorders	48	88.9
Nervous system disorders	41	75.9
General disorders and administration site conditions	23	42.6
Gastrointestinal disorders	18	33.3
Ear and labyrinth disorders	17	31.5
Social circumstances	10	18.5
Injury, poisoning and procedural complications	9	16.7
Skin and subcutaneous tissue disorders	8	14.8
Infections and infestations	7	13
Investigations	5	9.3
Metabolism and nutrition disorders	4	7.4
Musculoskeletal and connective tissue disorders	4	7.4
Cardiac disorders	3	5.6
Endocrine disorders	3	5.6
Respiratory, thoracic and mediastinal disorders	3	5.6
Immune system disorders	2	3.7
Renal and urinary disorders	2	3.7
Vascular disorders	2	3.7
Eye disorders	2	3.7
Blood and lymphatic system disorders	1	1.9

Note: Each report may have more than one adverse drug reactions and each adverse drug reaction can represent in more than one system organ classes.

The most reported adverse drug reactions with tafenoquine is depression (55.6 %), followed by anxiety (48.1 %), paranoia (29.6 %) and anger (27.8 %) as described in Table 5.

Table 5 Numbers of adverse drug reactions associated with tafenoquine in the WHO VigiBase™

Adverse drug reaction	Number	Percentage
Depression	30	55.6
Anxiety	26	48.1
Paranoia	16	29.6
Anger	15	27.8
Amnesia	14	25.9
Tinnitus	14	25.9
Nightmare	13	24.1
Post-traumatic stress disorder.	13	24.1
Suicide attempt	12	22.2
Disturbance in attention	11	20.4

Note: Each report may have more than one adverse drug reaction.

Chapter 4

Pharmacovigilance methods for monitoring the safety profile of tafenoquine

Safety data of tafenoquine is limited. As of 28th October 2018, approximately 4,000 participants were enrolled in tafenoquine-related clinical studies, including ten phase I studies, nine phase II / III studies, and three phase III studies.[7]

Since 2018, tafenoquine has received marketing authorization approvals in four countries. In Thailand, tafenoquine (Krintafel®) has just been approved at the end of the year 2019 as a conditional approval new drug, with a safety monitoring program requirement. Patients taking tafenoquine should be monitored for the safety of their use.

The pharmacovigilance method of tafenoquine for health care professionals (HCPs) used in hospitals is targeted spontaneous reporting. Patients taking tafenoquine are monitored as part of clinical practice to capture all adverse events, either serious or non-serious during 2020 - December 2022 with the operation guide as follows.

1. Healthcare Professionals (HCPs) including physicians, pharmacists and nurses are informed these guidelines on monitoring and capturing adverse events to tafenoquine. Then, they plan a suitable monitoring method in details for their hospitals.

2. Pharmacists who play a major role in pharmacovigilance in each hospital should be notified the information of patient prescribed tafenoquine.

3. Before dispensing the medicine, pharmacists should provide counseling on adverse drug reactions of tafenoquine that may occur to the patients.

4. The patients are monitored and detected adverse event(s) associated with tafenoquine by pharmacists.

5. When patients develop any suspected adverse event(s) associated with tafenoquine (serious or non-serious adverse events), the following actions should be performed.

5.1. <u>In-patient cases</u>

When a patient has suffered from any abnormal sign(s) or symptom(s) such as abnormal paleness and dark-colored urine, a nurse should inform a physician and a pharmacist. These may be signs of hemolytic anemia, suspected adverse events to tafenoquine.

5.2. Out-patient cases

When a patient has had suspected adverse event(s) after taking tafenoquine given either from the hospital or out of the hospital, a physician who find the event(s) should notify or assign a nurse to notify a pharmacist.

6. After notified, a pharmacist should investigate all relevant patient information including concomitant medicines and medical records to perform causality assessment of adverse event(s) to the suspected drug(s).

7. If the event is an adverse drug reaction to tafenoquine, the pharmacist should document it in the patient's medical record and provide a drug alert card to the patient.

8. Pharmacist responsible for reporting adverse event(s) of tafenoquine to the Thai FDA should submit the report to the Thai FDA according to the following requirements.

8.1. Reporting time frame

When any adverse event of tafenoquine is detected, either serious or non-serious, it should be reported as soon as possible as the following time frame.

1) For fatal outcome or unlabeled/unexpected adverse drug reactions associated with tafenoquine, the reporter should send an initial report of the events to the Thai FDA immediately by phone or email **within one business day** after first acknowledgement and submit a complete report within 7 calendar days.

2) For other fatal outcomes apart from 1), the reporter should send an initial report of the events as soon as possible but no later than 7 calendar days after first acknowledgement, and submit a complete report within 8 additional calendar days.

3) For serious events except for fatal outcome, the reporter sends an initial report of the events within 15 calendar days and submit a follow-up report within 30 calendars whenever receiving additional information.

4) For non-serious events, the reporter sends an initial report of the events within two months and submit a follow-up report within two months whenever receiving additional information.

After submitting the initial report, follow-up information should be actively sought and submitted to the Thai FDA when it becomes available. The reporter should identify the follow-up number and identification number (HPVC No.) of the initial report generated by the Thai FDA, if known. The initial and follow-up reports on the same case have the same HPVC No.

8.2 Reporting channels

The reporter can submit adverse event reports of tafenoquine via two channels as follows.

1) AE online reporting system

The reporter can report the adverse events using the electronic form (E-form) designated by the Thai FDA. The E-form can be downloaded from the HPVC website and submitted to the Thai FDA online portal (OpenID system). The reporter can study details of submission method of adverse event reports using E-form from "Guidance on the submission method of adverse event reports"
at http://thaihpvc.fda.moph.go.th/thaihvc/Public/Webpage/main.jsp

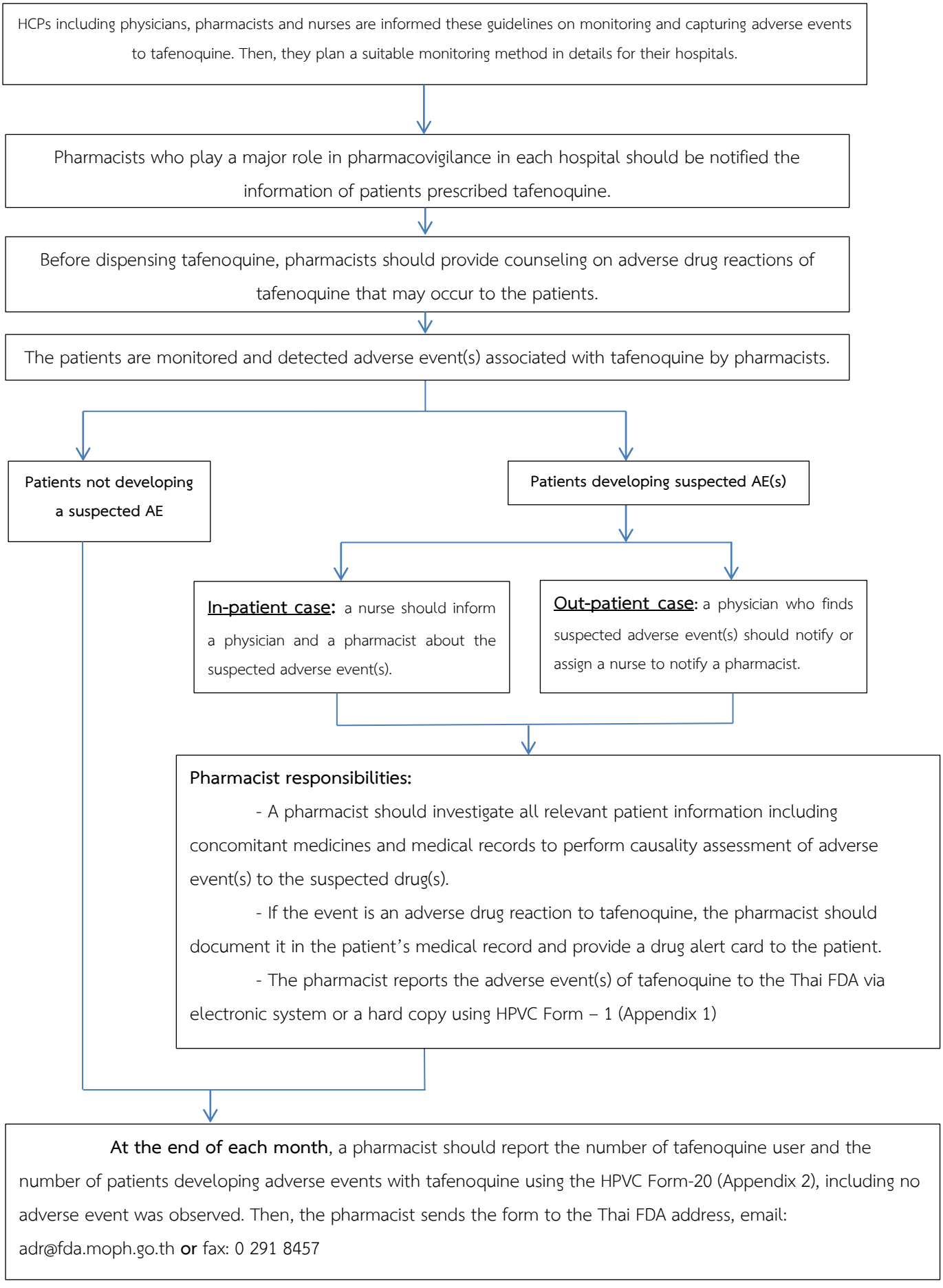
2) Document format

The reporter can report adverse events using the Adverse Event on Health Product Reporting Form (HPVC form -- Appendix 1) designated by the Thai FDA. The form can be downloaded from the following website http://thaihpvc.fda.moph.go.th/thaihvc/Public/Webpage/main.jsp. The adverse event reports have to be sent to

- Health Product Vigilance Center, Strategic and Planning Division, Thai Food and Drug Administration, Ministry of Public Health, Talat Khwan, Muang, Nonthaburi, 11000 **or**
- Fax: 0 2591 8457 **or**
- E-mail: adr@fda.moph.go.th

9. At the end of each month, a pharmacist should report the number of tafenoquine users and the number of patients developing adverse events associated with tafenoquine using the HPVC Form-20 (Appendix 2). If no patients experienced adverse events, the pharmacists should report zero event in the HPVC Form-20. Then, the reporter sends it to the address, email **or** fax as mentioned above.

Figure 3 Operational flowchart for monitoring the safety profile of tafenoquine



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Appendix 1

Health Product Adverse Event Report Form

HPVC No. ..... Reference no. of reporter/source of report.....

Health Product Adverse Event Report Form

(all information will be held confidentially by the government)

❑ Initial ❑ Follow up No.....

Reference No.....

Source of Report ❑ Spontaneous Reporting ❑ Intensive Monitoring ❑ Clinical Trial

Patient Information

Patient ID ❑ HN..... ❑ AN.....	**Patient type** ❑ IPD ❑ OPD	**Race** ❑ Thai ❑ Other (specify)	**Age**	**History of allergies** ❑ No ❑ Yes (please specify).....
Patient Initials (first, last)	**Gender** ❑ Male ❑ Female	.....	**Weight**	**Underlying disease / other relevant conditions** (specify ICD code, if known) .....

Health Product Information

Type of Health Product ❑ drug/narcotics and psychotropic substance ❑ new drug (SMP) ❑ food ❑ cosmetic ❑ medical device ❑ hazardous substance

Product name (Generic name/Trade name, dosage form, lot no. and exp. date for biological product, and part use for herbal product)	S, O, I *	Dose and Administration (strength, quantity, unit, frequency, route)	Starting date (d/m/y)	Discontinuing date (d/m/y)	Disease/reason for use (specify ICD code, if known)	Source of product (1 or 2)

* **S** = suspected product, **O** = other / concomitant product, **I** = product interaction

Source of product: 1 = hospital, 2 = other source (please specify)

Adverse Event Information

Adverse Events (describe event and/or technical term)	Labeled or non-labeled ADR	Positive laboratory findings and physical evidence
Date of onset (d/m/y).....		

Seriousness
- ❑ Non-serious
- ❑ Serious (choose only one)
  - ❍ Death (d /m /y).....
  - ❍ Life-threatening
  - ❍ Hospitalization-initial or prolonged
    - △ in-patient hospitalization
    - △ prolongation of hospitalization
  - ❍ Persistent or significant disability/incapacity
  - ❍ Causes a congenital anomaly/birth defect
  - ❍ Medical significant (please specify) .....

❑ **Dechallenge**
- ❍ Definite improvement
- ❍ No improvement
- ❍ Unknown

❑ **Continued use**
- ❍ Same dose
- ❍ Reduced dose
- ❍ Changed administration

❑ **Rechallenge**
- ❍ Recurrence
- ❍ No recurrence
- ❍ Unknown

❑ **No rechallenge performed**

Outcome (after the adverse event)
- ❑ Recovered without sequelae
- ❑ Recovered with sequelae
- ❑ Recovering
- ❑ Not yet recovered
- ❑ Died -
  - ❍ due to adverse reaction
  - ❍ drug may be contributory
  - ❍ unrelated to drug (please specify) .....
- ❑ Loss of follow up

Source of Event/Reporter Information

Person making diagnosis .....

Occupation ❑ Physician ❑ Pharmacist ❑ Nurse ❑ Other (please specify) .....

Evaluator/reporter .....

Occupation ❑ Physician ❑ Pharmacist ❑ Nurse ❑ Other (please specify) .....

Date of report (d/m/y).....

Source of event.....

Province.....Telephone No.....

Source of reporter.....

Province.....Telephone No.....

Cause of Event

❑ **Product reaction (ADR/vaccine reaction)** - Causality assessment categories
- ❍ Certain
- ❍ Probable
- ❍ Possible
- ❍ Unlikely
- ❍ Unclassified (please specify reason) .....

❑ **Medication error**
❑ **Programmatic error** (vaccine)
❑ **Coincident** (vaccine)
❑ **Product defect**
❑ **Accident**
❑ **Suicide**
❑ **Misuse/inappropriate use**
❑ **Other** (please specify reason) .....
.....

1

HPVC Form - 20

Appendix 2

Summary report form for monitoring the safety profile of tafenoquine

Hospital.....Province.....

Month/Year.....Number of patients taking tafenoquine.....

Number of patient taking tafenoquine and experiencing adverse events.....

Number	HPVC Number	Date of report submission	Notes
Reporter name.....		Date of reporting.....	
Telephone number		E-mail:.....	